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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,391	11/22/2000	Richard G. Vile	07039-294001	3279

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EXAMINER	
CHEN, LIPING	
ART UNIT	PAPER NUMBER
1632	

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10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/721,391	Applicant(s) VILE ET AL.	
	Examiner Liping Chen	Art Unit 1632	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-33 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-33 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the claims

Claims 1-33 are pending and examined in this office action on the merits.

Priority

This application is filed on 11/22/2000).
Priority claimed to provisional application 60/167,085 filed 11/23/1999.

Objection

The disclosure is objected to because of the following informalities:

Description of the drawings for Figure 3A is objected because it states "under the control of the Thr11 base pair promoter" (page 5, line 12). This should be written as "under the control of the Thr115 base pair promoter".

Description of the drawings for Figure 4 is objected because it repeats twice (page 5, line 19-29 and page 6, line 1-13).

Description of the drawings for Figure 9 (page 7, line 5-11) is objected because it is not in consistence with Example 7 (page 37, lane 12-14). It is not clear which lanes in Figure 9B are the samples after heat shock.

The label for Figure 10B is objected because it is not clear which construct is used for lane 4 and lane 5.

Description of the drawings for Figure 13 cannot correctly reflect the data. Each figures (13A-D) under the Figure 13 has data related with different construct. It is suggested to rewrite the description to clearly indicate the invention.

P14, line 18, containing (http://www.genome.ad:jp/SIT/TFSEARCH) is objected to because it contains an embedded hyperlink. Applicant is required to delete the embedded hyperlink. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

DJR 8/22/02

Claims 3, 14 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is: any gene which encodes a gene product having killing function in claim 1, such as cytotoxic gene.

Claim 24, as written is depended on any one of claims 15-17. However, claim 24 is directed to a nucleic acid molecule, claims 15-17 are directed to compositions. Thus, the dependence is improper.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 and 27-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Tyr300 promoter operably linked to a cytotoxic gene for killing melanoma cells by local infection, does not reasonably provide enablement for treating a patient in need of tissue-selective gene therapy for any diseases using the same vector or a two component vector system with HSE/HSF-1 regulation *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is directed to treating a patient in need of tissue-selective gene therapy by administering to a patient a composition comprising a nucleic acid molecule that comprising a cell type-specific promoter, a therapeutic gene sequence operable linked to cell type-specific promoter, an amplification promoter element, and a sequence encoding a transcription activator; and the composition.

The specification emphasizes that the use of cell type-specific promoters to induce the expression of cytotoxic agents in tumor cells is particularly problematic.

The higher the potency of the suicide gene, such as GALV applied, the greater the potential damage to non-tumor cells that receive the gene if the promoter controlling the suicide gene is not perfectly tumor-specific (page 2, line 10-13 and line 23-26). Applicant address that the instant invention is to enable the gene expression in a target tissue at least 100-fold higher or 1000-fold higher than if the construct is expressed in a non-target tissue (specification, page 3, line 18-20) and the transgene expression can be controlled by positive feedback such as using heat shock element (specification, page 3, line 23 to page 4, line 2). However, the specification only provides a list of cell type promoter (specification, page 12, line 6-page 13, line 15), a list of transgene including genes encoding fusogenic proteins (specification, page 23, line 20 to page 26, line 9) can be used for treating cancer, the examples using cultured cells with a transgene construct such as using cells to determine Tyr300 promoter is melanoma cell specific (specification, page 32, Example 1 and Figure 3), using melanoma MeWo cells transfected with the Tyr300-GM-CSF or the HSE-Tyr300-Full-GM-CSF by comparing with non-melanoma cell HT1080) to determine Tyr300 promoter is significantly induced in melanoma cell by HSF-1 (specification, page 6, page 32-33, Example 2 and Figure 4), or using separated cell lines such as non-melanoma TelCeB6 cells and melanoma Me1624 cells to demonstrate the specific GALV protein expressed by the control of Tyr300 promoter, this specificity is increased when regulated by HSF-1 with a deletion of amino acid residues of 202-316 (specification, page 8, page 39, Example 10 and

Figure 13). The only *in vivo* data showed is using nude mice model by introducing tumors with different promoter encoding GALV gene with the result of no regrowth of tumors when the TYR-GALV plasmid is used (specification, page 34-35, Example 4 and Figure 7). This is not correlated with introducing any vector to any animal or a patient for treating any tumor or disease encompassed by the claim. The specification does not provide evidence or guidance for regulation of any transgene expression *in vivo*. There is also no evidence that any construct especially construct encoding a cytotoxic gene can have the transgene expression to reach 100-fold higher in the gene expression level under any promoter in any target cell than non-targeted cells *in vivo* (pertaining to instant claims 15-17). Moreover, at the time of filing Gura et al. (Science, 278:1041-1042, 1997) teach that the growth of human tumors in immunocompromised mice does not reflect the natural and physiological growth and spread of tumors in non-immunocompromised animals so that "drugs tested in the xenografts appeared effective but worked poorly in humans. " (Gura, page 1041, sec. col., sec. Full parag.). Moreover, Orkin et al. (Report for The Third Meeting of The NIH Investment in Research on Gene Therapy, August, 1995) states that "Unfortunately, however, mouse models often do not faithfuloly mimic the relevant human conditions (Orkin, page 11, sec. full parag.). Orkin et al. Further states that "animal models are not satisfactory for studying many important human disorders, including cystic fibrosis, various cancers, and AIDS. Therefore, human studies are necessary to develop effective treatments for these and many other

diseases" (Orkin, page 14, forth parag.). Further, the specification only provide a list of vector and method of delivery (specification, page 27, line 24 to page 29, line 2), there is no teaching as to use any specific vector for any specific transgene and specific route for delivery to any specific targeting cells.

The unpredictability in gene therapy has been widely recognized in the arts since the time of filing (Anderson, Nature 392:25-30, 1998; Nishikawa et al., Human Gene therapy 12:867-870, 2001, Rozenberg et al., S.T.P. Pharma Sciences 11:21-30, 2001; and Balicki, Medicine 81:69-86, 2002). Anderson (1998) teaches that the challenge of developing gene therapy as an efficient and safe drug-delivery system is more difficult to achieve than many investigators had predicted. The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome (Anderson, page 25, left col. sec. parag.). Rozenberg et al. (2001) teach that the choice of gene delivery vector is a key factor for the success of gene therapy application. It determines the efficiency of the gene packaging, unpackaging, expression and delivery to the site of interest (Rozenberg, Abstract). Balicki (2002) compares several vectors, such as Retrovirus, Adenovirus, Lentivirus, Adno-Associated Virus, Herpes Simplex Virus in different generation as well as liposome, protein/peptide and naked DNA, by means of cell target, chromosomal integration and immunogenicity (Balicki, page 70, Table 1) and teaches that the most common and useful strategy is to deliver the gene of interest to the nucleus and points out

the extracellular barriers for such delivery include degradative enzymes (Balicki, page 70, left col. first parag.). Further, Nishikawa et al (2001) teach that development of an efficient method for introducing a therapeutic gene into target cells *in vivo* is the key issue in treating genetic and acquired diseases by gene therapy (Nishikawa, Abstract). Nishikawa et al. further teach that the physicochemical properties of a DNA-vector complex will affect its passage through capillaried, extravasation, capture by the mononuclear phagocytes, and uptake by target cells (Nishikawa, page 862, col. 1 first full parag.). Taken together, the art teaches that gene delivery is specific by each vector and each encoded transgene for each cell target. It is noted that case law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not how to find out, how to use it, for themselves (see In re Gardner et al. 166 USPQ 138 (CCPA 1970). The specification only teaches what is intended to be done, but does not actually teach how to do that which is intended.

As the specification fails to provide any evidence or teaching to teach the skilled artisan how to use any vector such a vector comprising Tyr300 promoter to encode any transgene to any specific tissue of any animal so that the transgene expression can be regulated under the control of HSF-1 *in vivo* for treating any tumor or disease, the claimed methods are not enabled. Due to the lack of direction and guidance, unpredictable gene delivery in gene therapy, no evidence the composition described can result a cytotoxic transgene expression 100 to 1000 fold

in a target cell than non-target cells in a non-immunocompromised subject, no direction or guidance as how to use any transgene specifically with any vector for any specific type of cells, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation without a predictable degree of success to achieve any specific and the breath of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1,2, 4-7, 19, 21, 22, and 27 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Wu et al. (U.S. Patent 5,756,343, issued May 26, 1998).

Claims 1, 2, 4-7, 19, 21, 22 and 27 are directed to a composition comprising a nucleic acid molecule comprising a cell type-specific promoter, a therapeutic gene sequence operably linked to cell type-specific promoter, an amplification promoter element such as HSE (claim 7), and a sequence encoding a transcription activator, which is activated by a stressor (claim 19).

Wu et al. teach a multimerization vector comprising recombinant HSF gene, HSE gene, linked to a tissue-specific promoter (col. 10, line 1-4) for expression of any gene products (col. 9, line 50-67) for the regulation under chronic stress condition (col. 10, line 5). Wu et al. Further teach to increase expression of other gene products by cotransfecting HSF gene together with other genes linked to HSEs (pertaining to instant claim 6) (col. 10, line 9-11). Thus, Wu et al. clearly anticipates the claimed invention.

Claims 1, 2, 4-7, 11, 13, 21 and 25 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Baird et al. (U.S. Patent 6,037,329, issued March 14, 2000).

Claims 1,2, 4-7, 11, 13, 21 are directed to a composition comprising a nucleic acid molecule comprising a cell type-specific promoter, a therapeutic gene sequence operably linked to cell type-specific promoter, an amplification promoter element, and a sequence encoding a transcription activator; claim 25 is directed to a nucleic acid molecule comprising a human tyrosinase promoter operably linked to a cytotoxic gene.

Baird et al. ('329) teach to use a tissue-specific promoter such as human ('329, col. 75, line 22-24) tyrosinase promoter ('329, col. 26, line 44-46) for expression of DNA encoding cytotoxic agent such as cytosine deaminase ('329, col. 26, line 17-20, and col. 6, line 15-29, pertaining to claim 25). Baird et al. further teach to use

inducible promoter (col. 27, line 47-54) for multiple delivery system for inducing cytotoxic agent expression such as using a heat shock promoter to direct cytocide encoding agent expression, which can be induced by a second construct encoding a gene elicite SOS pathway, and the both construct could be merged into one construct ('329, col. 29, line 15-50). Thus, Baird et al. clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 8, and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (U.S. Patent 5,756,343, issued May 26, 1998) in view of Baird et al. (U.S. Patent 6,037,329, issued March 14, 2000) further in view of Russell et al. (U.S. Patent Application US 2002/0042147 A1, published April 11, 2002).

Claims 1, 3, 8 and 11-13, are directed to a composition comprising a nucleic acid molecule that comprising a cell type-specific promoter, which is a tumor type promoter (claim 3) selectively active in melanoma cells (claim 8), a cytotoxic gene

(claim 11) such as cytosine deaminase) gene (claim 13) or a gene encodes a fusogenic protein (claim 12) operable linked to cell type-specific promoter, an amplification promoter element, and a sequence encoding a transcription activator.

Wu et al. ('343) teach a multimerization vector comprising recombinant HSF gene, HSE gene, linked to a tissue-specific promoter (col. 10, line 1-4) for expression of any gene products (col. 9, line 50-67) for the regulation under chronic stress condition (col. 10, line 5). However, Wu et al. does not specific teach to use the vector for cytotoxic gene expression.

However, Baird et al. ('329) teach to use a tissue-specific promoter such as human tyrosinase promoter ('329, col. 75, line 22-24) for expression of DNA encoding cytotoxic agent such as cytosine deaminase ('329, col. 6, line 15-29) for melanoma treatment ('329, col. 26, line 17-20 and line 44-46). Further, Russell et al teach using expression vector to express fusogenic protein to kill melanoma or other cancer cells (page 1, parag.[0017]).

With the knowledge of Wu et al. ('343) to use two component vector system for gene expression under tissue-specific promoter and HSE/HSF regulation, the knowledge of Baird et al. ('923) using specific tissue specific promoter, tyrosinase promoter, encoding cytotoxic agent for melanoma treatment, and the teaching of Russell et al to use fusogenic protein to kill melanoma, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Wu et al. by using designed tumor-specific promoter

such as tyrosinase promoter and a gene of interest such as cytosine deaminase gene of Baird et al. or a gene encoding a fusogenic protein of Russell et al. in order to better regulate the expression of the gene of interest such as a gene encoding fusogenic protein for more specifically killing cancer cells such as melanoma when using the two component system of Wu et al. ('343) given results of Baird et al. ('923) and Russell et al.

Claims 1, 3, 8, and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (U.S. Patent 5,756,343, issued May 26, 1998) in view of Vile et al. (Cancer Res. 54:6228-6234, 1994) further in view of Russell et al. (U.S. Patent Application US 2002/0042147 A1, published April 11, 2002).

Claims 1, 3, 8 and 11-13, are directed to a composition comprising a nucleic acid molecule that comprising a cell type-specific promoter, which is a tumor type promoter (claim 3) selectively active in melanoma cells (claim 8), a cytotoxic gene (claim 11) such as HSVtk gene (claim 13) or a gene encodes a fusogenic protein (claim 12) operable linked to cell type-specific promoter, an amplification promoter element, and a sequence encoding a transcription activator.

Wu et al. ('343) teach a multimerization vector comprising recombinant HSF gene, HSE gene, linked to a tissue-specific promoter (col. 10, line 1-4) for expression of any gene products (col. 9, line 50-67) for the regulation under chronic stress

condition (col. 10, line 5). However, Wu et al. does not specific teach to use the vector for cytotoxic gene expression.

However, Vile et al. (1994) teach using a vector comprising tissue specific tyrosinase promoter (pertaining to instant claims 2,3,8 and 9) for the expression of HSVtk cytotoxic gene (pertaining to instant claims 11 and 13) in primary murine melanoma tumor (Vile, Abstract and page 6229, Figure 1) for killing tumor. Further, Russell et al teach using expression vector to express fusogenic protein to kill melanoma or other cancer cells (page 1, parag.[0017]).

With the knowledge of Wu et al. ('343) to use two component vector system for gene expression under tissue-specific promoter and HSE/HSF regulation, the knowledge of Vile et al. using specific tissue specific promoter, tyrosinase promoter, encoding cytotoxic agent for melanoma treatment, and the teaching of Russell et al to use fusogenic protein to kill melanoma, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Wu et al. by using designed tissue-specific or tumor-specific promoter such as tyrosinase promoter and a gene of interest such as HSVtk gene of Vile et al. or a gene encoding a fusogenic protein of Russell et al. in order to better regulate the expression of the gene of interest such as a gene encoding fusogenic protein for more specifically killing cancer cells such as melanoma when using the two component system of Wu et al. ('343) given results of Vile and Russell.

Claims 1 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (U.S. Patent 5,756,343, issued May 26, 1998) in view of Miyanobara. (U.S. Patent 5,739,018, issued April 14, 1998), further in view of Russell et al. (U.S. Patent Application US 2002/0042147 A1, published April 11, 2002).

Claims 1 and 11-13, are directed to a composition comprising a nucleic acid molecule that comprising a cell type-specific promoter, a cytotoxic gene (claim 11) such as gene encoding an envelope protein of VSV G or GALV (claim 13) or a gene encodes a fusogenic protein (claim 12) operable linked to cell type-specific promoter, an amplification promoter element, and a sequence encoding a transcription activator.

Wu et al. ('343) teach a multimerization vector comprising recombinant HSF gene, HSE gene, linked to a tissue-specific promoter (col. 10, line 1-4) for expression of any gene products (col. 9, line 50-67) for the regulation under chronic stress condition (col. 10, line 5). However, Wu et al. does not specific teach to use the vector for cytotoxic gene expression.

Miyanobara et al. ('018) teach to use an inducible tissue-specific promoter to express cytotoxic envelope protein ('018, col. 3, line 59-61 and col. 4, Line 22-23) such as envelope protein of VSV G and GALV ('018, col. 7, line 52-56).

Further, Russell et al teach using expression vector to express cytotoxic fusogenic protein to kill melanoma or other cancer cells (page 1, parag.[0017]).

With the knowledge of Wu et al. ('343) to use two component vector system for gene expression under tissue-specific promoter and HSE/HSF regulation, the knowledge of Miyanobara et al. ('923) to use inducible tissue specific promoter to encode cytotoxic envelope protein such as VSV G and VALV and the teaching of Russell et al to use fusogenic protein of viral envelope protein to kill melanoma and other cancers, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Wu et al. by using designed tissue-specific promoter and a gene of interest such as gene encoding a cytotoxic envelope protein of VSV G or GALV of Miyanobara et al. or a fusogenic protein of Russell et al. in order to better regulate the expression of the gene of interest such a gene encoding VSV G or GALV or fusogenic protein for more specifically killing cancer cells when using the two component system of Wu at al. ('343) given results of Miyanobara et al. and Russell et al.

Claims 1, 10, 18, and 28, are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (U.S. Patent 5,756,343, issued May 26, 1998) in view of He et al. (Mol. Cell. Biol.18:6624-33, 1998) and Hata et al. (BBA 1397:43-55, 1998).

Claims 1, 10, 18 and 28, are directed to a composition comprising a nucleic acid molecule that comprising a cell type-specific promoter, therapeutic gene operable linked to cell type-specific promoter, an amplification promoter element

such as human HSE consensus sequence (claim 10), and a sequence encoding a transcription activator such as HSF-1 (claim 18 and 28).

Wu et al. ('343) teach a multimerization vector comprising recombinant HSF gene, HSE gene, linked to a tissue-specific promoter (col. 10, line 1-4) for expression of any gene products (col. 9, line 50-67) for the regulation under chronic stress condition (col. 10, line 5). Wu et al. does not specific teach to use Consensus heat shock element sequence and HSF-1 gene as activator.

However, Hata et al. discloses human Hsp40 gene contains the consensus heat shock element sequences which is bound by HSF-1 factor (Hata, page 43, abstract).

Moreover, He et al. teach a regulation of HSF-1 transcription activity including a down regulation by glycogen synthase kinase 3beta and extracellular signal-regulated kinase mitogen-activated protein kinase resulted a reduced hsp-70 transcription after hear shock.

With the knowledge of Wu et al. ('343) to use two component vector system for gene expression under tissue-specific promoter and HSE/HSF regulation, the knowledge of Hata et al. that HSE consensus sequences is bound by HSF-1, and the teach of He et al. that HSF-1 can be down regulated by enzymes such as glycogen synthase kinase 3beta, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Wu et al. by using at least one human HSE consensus sequence of Hata et al. and

using a subtype of HSF, HSF-1taught by He et al., in order to regulate the expression of a gene of interest by both activation and inhibition the activation for better control the expression of the gene of interest when using the two component system of Wu et al. ('343) given results of Hata et al. and He et al.

Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (In Vivo 13:181-187, March-April,1999) in view of Russell et al. (U.S. Patent Application US 2002/0042147 A1, published April 11, 2002) further in view of Takeda et al. (Biochem. Biophys. Res. Comm. 162:984-990, 1989).

Cao et al. (1999) teach using a vector comprising murine (Cao, page 181, right col. sec. full parat. and Materials and Methods) tissue specific tyrosinase promoter for the expression of cytosine deaminase gene for in vivo gene therapy using C57BL/6 mice with disseminated melanoma (Cao, page 181, abstract and page, 185, Figure 3). Russell et al teach using expression vector to express fusogenic protein to kill melanoma or other cancer cells (page 1, parag.[0017]). Both Cao and Russell do not teach using human tyrosinase promoter.

However, Takeda et al. teach expressing human tyrosinase gene with a part of exon 1 (Takeda, page 988, last parag. and Figure 2), which contains Try300 promoter at nucleic acids 124-423 (see attached sequence search result), in mouse K1735 amelanotic melanoma cells for the human tyrosinase gene characterization

in order further study the human gene isolated from a patient (Takeda, page 989, bridg parag.).

With the knowledge of Cao et al. using murine tyrosinase promoter encoding cytotoxic gene for melanoma treatment in mouse model and the teaching of Russell et al to use fusogenic protein to kill melanoma, and the teaching of Takeda et al. to use human tyrosinase promoter for treating human patient, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Cao et al. by substituting a human tyrosinase promoter of Takeda et al. for a murine tyrosinase promoter to encode fusogenic protein of Russell et al. to kill malanoma or other cancer cells in human patient given results of Russell et al and Takeda et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liping Chen, whose telephone number is (703) 305-4842. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time). Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Pauline Farrier, Patent Analyst, at (703) 305-3550. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

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